Team Number: THS159
School Name: Taos High School
Area of Science: Biology and Medicine & Health
Project Title: MytoSensor: Measuring mitochondrial toxicity and dysfunction within cells to detect disease.
Team Members: Delaney Galligan & Sierra Ferguson

Problem Definition:

Mitochondria are the powerhouses of the cell, but when something goes wrong, the mitochondria is responsible for cellular dysfunction. When the dysfunction is caused by outside sources, it is called mitochondrial toxicity, when it is caused by genetic sources, it is called mitochondrial dysfunction. The glycolytic and ATP progression in mitochondria produces electrical impulses, known as conductivity and resistivity, which in turn can be used as a wearable testing device to determine changes in body health. This has been experimented by our team for several years. The final product we are hoping to produce would be a lightweight, wearable sensor that is sensitive enough to detect cell signaling and galvanic cell response and relay this in real-time to a phone app to indicate immediate cellular impact, which would enable the user to take action to reverse the toxicity at the cellular level to avoid disease progression. The overall goal is to produce a fully functioning 3D model that shows how this sensor would work at the cellular level.

Problem Solution:

From this experimentation and data, our team is attempting to see if we can produce a database of cellar/mitochondrial reactions as indicators of disease/toxicity via mitochondria dysfunction from our scientific findings and enter into a 3D model. This model will provide a quicker way of gaining data and seeing if the sensor works. In doing this, our model needs to have a full library of ATP/electro activity that occurs within the mitochondria and cells during homeostasis and different diseases. This model will also help with reducing the confusion between electrodermal and electrocellular feedback.

Progress to Date:

As of right now, experimentation has been continued to add to the growing database of cellular and mitochondrial reactions from different diseases and levels of toxicity. We are actively working on entering the results into the database. We are also working on coding the 3D model of the mitochondria the cell and their processes. We are also conducting a massive amount of research to better understand our scientific findings and what needs to go into the model. We have also started collaborating with different mentors who have been helping us with refining our research and understanding the findings which we then put into the database.

Research to Date:

Galvanic Skin Response/Electrodermal activity (EDA)

Electrodermal activity (EDA), is the property of the human body that causes continuous variation in the electrical characteristics of the skin. Historically, EDA has also been known as skin conductance, galvanic skin response (GSR), electrodermal response (EDR), psychogalvanic reflex (PGR), skin conductance response (SCR), sympathetic skin response (SSR) and skin conductance level (SCL) (Boucsein, 2012).

The traditional theory of EDA indicates that skin resistance varies with the state of sweat glands in the skin. Sweating is controlled by the sympathetic nervous system, and skin conductance is an indication of psychological or physiological arousal. If the sympathetic branch of the autonomic nervous system is highly aroused, then sweat gland activity also increases, which in turn increases skin conductance. In this way, skin conductance can be a measure of emotional and sympathetic responses. The study of EDA has led to such important and vital tools as the electrocardiograph (ECG or EKG) and the electroencephalograph (Boucsein, 2012).

Human extremities, including fingers, palms, and soles of feet display different bio-electrical phenomena. They can be detected with an EDA meter, a device that displays the change electrical conductance between two points over time. The two current paths are along the surface of the skin and through the body. Active measuring involves sending a small amount of current through the body. Some studies include the human skin's response to alternating current, including recently deceased bodies. There is a relationship between emotional arousal and sympathetic activity, although the electrical change alone does not identify which specific emotion is being elicited. These autonomic sympathetic changes alter sweat and blood flow, which in turn affects GSR and GSP. The response of the skin and muscle tissue to external and internal stimuli can cause the conductance to vary by several microsiemens or minutely microvolts. A correctly calibrated device can record and display the subtle changes (Boucsein, 2012).

The combined changes between electrodermal resistance and electrodermal potential make up electrodermal activity. Galvanic skin resistance (GSR) is an older term that refers to the recorded electrical resistance between two electrodes when a very weak current is steadily passed between them. The electrodes are normally placed about an inch apart, and the resistance recorded varies according to the emotional state of the subject. Galvanic skin potential (GSP) refers to the voltage measured between two electrodes without any externally applied current. It is measured by connecting the electrodes to a voltage amplifier. This voltage also varies with the emotional state of the subject. A painful stimulus such as a pinprick elicits a sympathetic response by the sweat glands, increasing secretion. Although this increase is generally very small, sweat contains water and electrolytes, which increase electrical conductivity, thus lowering the electrical resistance of the skin. These changes in turn affect GSR. Another common manifestation is the vasodilation (dilation) of blood vessels in the face, referred to as blushing, as well as increased sweating that occurs when one is embarrassed. EDA is highly responsive to emotions in some people. Fear, anger, startled response, orienting response, and sexual feelings are among the reactions that may be reflected in EDA. These responses are utilized as part of the polygraph or lie detector test. EDA in regular subjects differs according to feelings of being treated fairly or unfairly, but psychopaths have been shown to manifest no such differences. This indicates that the EDA record of a polygraph may be deceptive in a criminal investigation (Boucsein, 2012).

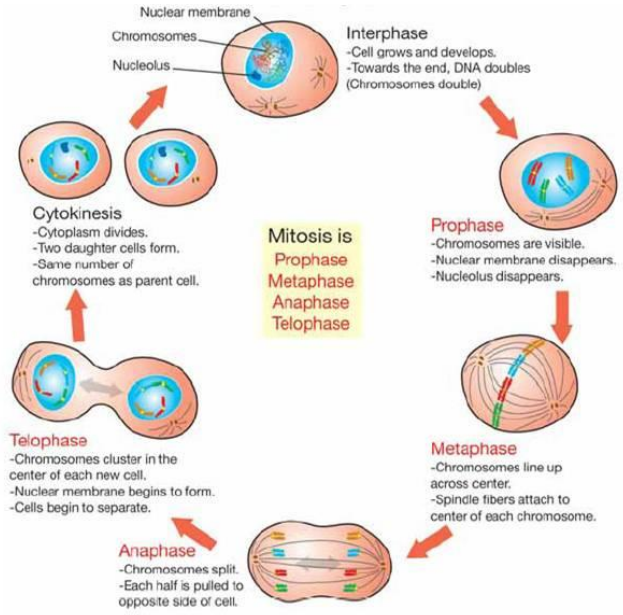
EDA is a common measure of autonomic nervous system activity, with a long history of being used in psychological research. Many biofeedback therapy devices utilize EDA as an indicator of the user's stress response with the goal of helping the user to control anxiety. Oftentimes, EDA monitoring is combined with the recording of heart rate, respiratory rate, and blood pressure, because they are all autonomically dependent variables. EDA measurement is one component of modern polygraph devices, which are often used as lie detectors. EDA measurement is also becoming more popular in hypnotherapy and psychotherapy practices for detecting depth of hypnotic trance prior to the commencement of suggestion therapy. When traumatic experiences are recalled by the client, immediate changes in sweat rate can indicate that the client is experiencing emotional arousal (Boucsein, 2012).

External factors such as temperature and humidity affect GSR measurements, which can lead to inconsistent results. Internal factors such as medications can also change GSR measurements, demonstrating inconsistency with the same stimulus level. Lastly, galvanic skin responses are delayed 1–3 seconds (Boucsein, 2012).

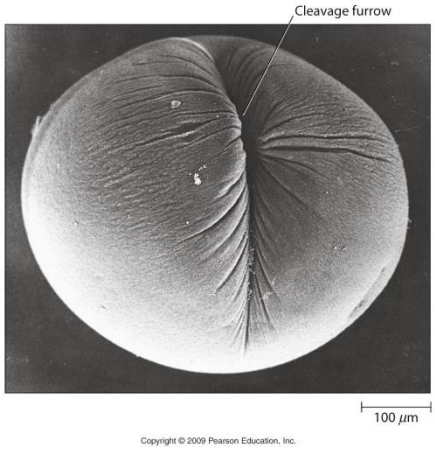
Cell Cycle

The human body relies on DNA within the nucleus of a cell to send out instructions for body functions and body energy usage. A huge amount of information resides within the DNA and through cellular reproduction processes can separate genetic material and share it via cell division. These methods are called mitosis and meiosis. Mitosis is a process that produces two cells, each of which is identical to the original parent cell. Mitosis is preceded by replication of the cell's DNA so each 'daughter cell' will have a full amount of genetic material. Traditionally in animals, mitosis is used for growth and repair of somatic body cells. This generally leads to asexual reproduction. Meiosis produces four cells from an original parent cell that is not identical to the parent cell, and only has half the parent cell's genetic matter. This is traditionally known as sexual reproduction. (Alters and Alters, 2008)

The cell cycle is the life cycle of the cell. These include prophase, pro-metaphase metaphase, anaphase telophase, interphase and cytokinesis. The cell cycle spends the most amount of time in interphase. This is the part of the cell cycle that includes cell growth, replication of cell organelles, replication of DNA, assembly of the parts of mitosis and the condensation of DNA. This phase is subdivided into stages G_1, S and G_2. The G_1 stage is the time gap between the last cell division and the start of DNA replication, during which time the cell is growing. This growth period occupies the major portion of the cell's lifespan, where the cell doubles its size and carries out its normal life functions. S (Synthesis) stage produces a complete replica of the cell's DNA for cell



division. By the end of this stage, the cell contains two complete, identical copies of the hereditary information. The G_2 stage signifies the time gap between the end of DNA replication and the beginning of cell division. The coils of DNA condense into tightly compacted masses that become visible chromosomes during mitosis. Each chromosome contains two copies of hereditary information in sister chromatids, connected by a centromere. Mitosis is a continuous sequence of events that occurs just after interphase, resulting in the separation of the sister chromatids. (Alters and Alters, 2008)



The first phase of mitosis, prophase is when the chromosomes have condensed. As prophase continues, the chromosomes continue to shorten and thicken. The nucleolus disappears because the cell is no longer capable of producing ribosomal RNA (rRNA). The microtubules (thin tubes of protein structures) are formed. The centrosome is the area in which these microtubules are organized. The centrosomes of animal cells begin to move away from each other in the beginning and by the end, each member of the pair has moved to an opposite end or pole of the cell. As the spindle fibers formulate, the nuclear membrane breaks down and the spindle fibers build a bridge between centrosomes from one pole to another. The spindle fibers then attach to kinetochores. This connection is critical to the separation and movement of sister chromatids during later stages of mitosis. The next stage of animal cell mitosis is metaphase. This occurs when the pairs of sister chromatids align in one plane at the center of the cell. This will indicate where the future plane of the cell division will be. After metaphase comes anaphase. In this phase, the sister chromatids are pulled in two different directions simultaneously. The chromatids separate into chromosomes and move rapidly toward opposite poles of the cell. They are pulled by the kinetochore by attached and shortening microtubules. This separation produces duplicate sets of hereditary material. The final phase, telophase is the preparation of the cell for cytokinesis. The spindle fibers are chemically disassembled and disappear. The nuclear envelope reforms around each set of chromosomes, which begin to uncoil, and the nucleolus reappears as rRNA. This phase is like prophase in reverse order. (Alters and Alters, 2008)

Mitosis is complete after telophase. The process of cell division is not. The portion of the cell outside the nucleus; cytoplasm is divided starting in telophase and completed in cytokinesis, where the separation of one cell into two takes place. In animal cells, this occurs by pinching the cell in two by a belt of microfilaments encircling the cell at the metaphase stage. As the microfilaments contract, a cleavage furrow appears around the circumference of the cell. As the contraction proceeds the furrow deepens until the opposing edges of the cell membrane make contact with one another. The membranes fuse, producing the cell separation. (Alters and Alters, 2008)

Mitochondrial toxicity

Condition in which the mitochondria of a body's cells become damaged or decline significantly in number; it commonly occurs as a side effect of certain antiretroviral drugs used to treat human immunodeficiency virus, or HIV, but has also been found in certain other drugs that target

proteins, amino acid production, RNA and DNA functions within the body as part of their function, such as some high impact, broad spectrum antibiotics.

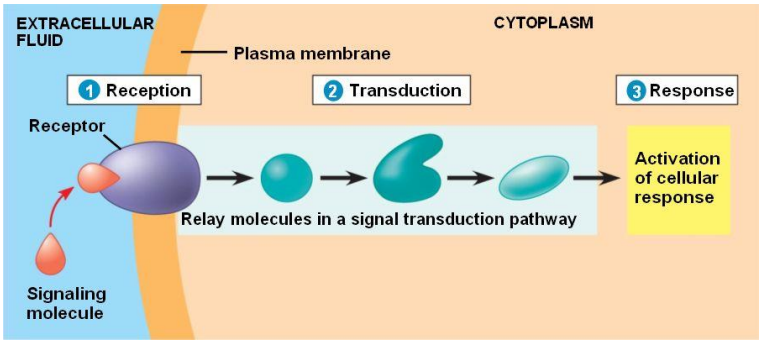
Mitochondrial toxicity leads to disease, illness and potentially death. It is also an emerging factor in drug resistance. The disruption of cell function that accompanies the condition can cause both mild and severe problems in people suffering from mitochondrial toxicity. The most commonly observed symptom is muscle weakness, or myopathy and lactic acidosis, though other ailments including ulcers, lupus and many 'mystery diseases' can be eventually attributed to this syndrome. Other symptoms include peripheral neuropathy (numbness in the fingers and toes) and pancreatitis (inflammation of the pancreas), with the most severe being lactic acidosis, in which a build-up of lactic acid in the tissues of the body leads to loss of energy, organ failure, and eventually death (Alberts, Johnson, Lewis, et. al., 2002).

Mitochondria

The mitochondrion (plural mitochondria) is a double membrane-bound organelle found in all eukaryotic organisms. Some cells in some multicellular organisms may lack them (mature mammalian red blood cells). A number of unicellular organisms, such as microsporidia, parabasalids, and diplomonads, have also reduced or transformed their mitochondria into other structures. Mitochondria generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy. Mitochondria are commonly between 0.75 and 3 μm in diameter but vary considerably in size and structure. Unless specifically stained, they are not visible. In addition to supplying cellular energy, mitochondria are involved in other tasks, such as signaling, cellular differentiation, and cell death, as well as maintaining control of the cell cycle and cell growth. Mitochondrial biogenesis is in turn temporally coordinated with these cellular processes. Mitochondria have been implicated in several human diseases, including mitochondrial disorders, cardiac dysfunction, heart failure and autism. The number of mitochondria in a cell can vary widely by organism, tissue, and cell type. For instance, red blood cells have no mitochondria, where liver cells can have more than 2000. The organelle is composed of compartments that carry out specialized functions. These compartments or regions include the outer membrane, the intermembrane space, the inner membrane, and the cristae and matrix. Although most of a cell's DNA is contained in the cell nucleus, the mitochondrion has its own independent genome that shows substantial similarity to bacterial genomes. Mitochondrial proteins (proteins transcribed from mitochondrial DNA) vary depending on the tissue and the species. In humans, 615 distinct types of protein have been identified from cardiac mitochondria, whereas in rats, 940 proteins have been reported. The mitochondrial proteome is thought to be dynamically regulated (Alberts, Johnson, Lewis, et. al., 2002).

Cell Signaling/Cell Voltage Change

Cell Signaling is a chemical response method in which one cell sends information to another cell through K+ Na+ pathways. This is also how cells communicate with each other, particularly when they are going through cell cycle changes or environmental stimuli changes. The mitochondria in their ATP production process communicate to other cells through cell membrane potential, a chemically reactive positive or negative charge that goes through one membrane to another. This also produces the noticeable cell voltage, through energy production from the electrolytes produced with ATP production. A higher level of resistance indicates homeostasis within the cell pathways and the stability of glycolysis, while a higher rate of conductivity shows instability in the cell cycle and pathways, therefore an interruption in the conductivity, through an excess of Na+ processing (Alberts, Johnson, Lewis, et. al., 2002).



Programmed Cell Death

Cancer and cellular toxicity causes mitochondria to be 'reprogrammed', and in the case of tumorigenic activity, the cells are encapsulated and oxygen is cut off, therefore forcing the mitochondria to work in anaerobic conditions, forcing glycolysis. Glycolysis is a series of biochemical reactions from which one molecule of glucose is oxidized to two molecules of pyruvic acid and a small amount of ATP. Increased activity in the glycolytic pathway is an indicator of disease in humans. Malignant, rapidly-growing tumor cells have glycolytic rates that are up to 200 times higher than those of their normal tissues of origin. (NCI, 2012)
Mitochondria are also suspected to play a role in the aging process. Once the mitochondria are forced into glycolysis, they continue to feed cancerous mutations. If these reprogrammed mitochondria are shut off or eliminated, then glycolysis can be shut down, and the surrounding cells can either escape the cancerous mutation cycle, or can be remediated. The mitochondria can also be re-reprogrammed to return to the production of ATP as a primary energy source, which cancerous material is not as prone to reproduce under. Cancerous material feeds off of sugar based chemicals for their energy source and relies heavily on carbohydrates, to reproduce biochemically. Certain chemicals interrupt these carbohydrate and anaerobic cycles, forcing oxygen into the reaction, and balancing off any free radical reactions (American Cancer Society, 2012).

Genetically programmed cell death (apoptosis, PCD), is one of the many concepts that is used to treat cancer. Some cells of the human body self-destruct after a limited lifespan, while others are programmed to last the lifetime of the organism. Those that self-destruct are replaced by the body with new cells produced from cell division of the survivors. Cancer is an indicator of a disruption of the cell's life cycle, where cells that should die do not and develop from failure of programmed cell death and divide uncontrollably. Apoptosis is a type of PCD in which cell suicide is pre-programmed; the cell membrane remains intact as the cell dies so that it does not release its contents and trigger a local inflammatory reaction. The dying cell splits into small membrane-bound bodies that are engulfed and digested by white blood cells. Many compounds have been tested as apoptosis agents (Alters and Alters, 2008).

Programmed Cell Death or PCD has had three main pathways identified: Type I: Apoptosis, Type II: Autophagisis and Type III: Necrosis. Apoptosis, as described above, is cell death produced by biochemical changes that lead to morphology changes and death. These morphology changes include blebbing, (irregular bulge in the plasma membrane caused by localized decoupling of the cytoskeleton from the plasma membrane) membrane cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. Apoptosis occurs naturally in the cell cycle, including in the development of body parts. Apoptosis is responsible for appendages such as fingers and toes to be separated, and can either lead to mutagenic qualities or death of the cell. This process produces cell fragments (apoptopic bodies) that phagocytic cells engulf and remove before the contents of the cell can spill out and cause damage in surrounding cells. The process of apoptosis can be controlled by a large and diverse range of cell signals that can originate extra-cellularly (extrinsic inducers) which include toxins, hormones, growth factors, nitric oxide or cytokines or intra-cellularly (intrinsic inducers). These inducers must either cross the plasma membrane or transducer to produce a response; the positive or negative triggering of apoptosis. The cell will initiate intracellular apoptopic signaling in response to stresses, which can potentially lead to a 'cell suicide'. The cell death is precipitated by enzymes, produced by the apoptopic signals that cause regulatory proteins to initiate apoptosis, which allows the selection of apoptosis in certain cells, or can stop the process should the cell no longer need to die. These two main methods of regulation are targeting mitochondria functionality, or transducing the signal through adaptor proteins to apoptopic mechanisms. Apoptosis occurs very quickly (NCI, 2011).

Viral proteins can cause intracellular stress which induces apoptosis. This response to internal stimuli causes a caspase cascade which in turn triggers a series of morphological changes within the cell. Once the caspase cascade has started, it is an irreversible process resulting in certain cell death. Apoptosis in HeLa cells is inhibited by proteins produced by the cell. Inhibitory proteins target retinoblastoma tumor suppressing proteins. These tumor suppressing proteins regulate the cell cycle, but are rendered inactive when bound to an inhibitory protein (Oyagbemi, et. al., 2010).

Apoptopic morphology is as follows:

1. **Cell shrinkage and rounding because of the breakdown of the proteinaceous cytoskeleton by caspases (executioner proteins). Cell swelling can also be noted.**
2. **The cytoplasm appears dense, and the organelles appear tightly packed.**
3. **Chromatin undergoes condensation into compact patches against the nuclear**

envelope (pyknosis)

4. **The nuclear envelope becomes discontinuous and the DNA inside it is fragmented. (karyorrhexis) The nucleus breaks into several discrete chromatin bodies or nucleosomal units due to the degradation of DNA.**

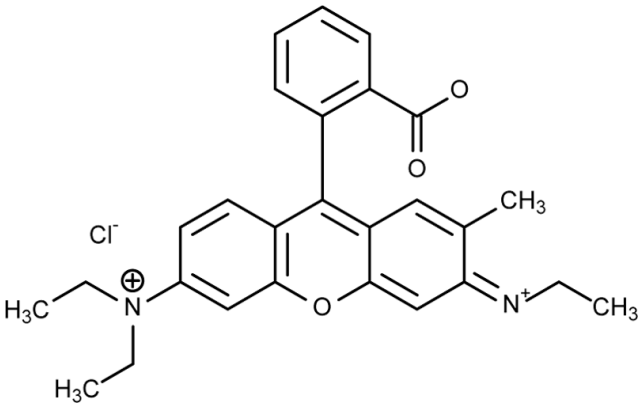
5. **The cell membrane shows blebs.**

6. **The cell breaks apart into several vesicles called apoptotic bodies, which are then phagocytosed (NCI, 2011).**

Type II PCD is autophagisis; a catabolic process that involves the degradation of a cell's components through lysosomal machinery, or the bursting of the cells' components through cellular damage. This is a tightly regulated process that is generally involved normally in cell growth, development and homeostasis. It helps to maintain a balance between the synthesis, degradation and subsequent recycling of cellular products. This is a mechanism where a starving cell can re-allocate nutrients from unnecessary processes to necessary ones (NCI, 2011).

Type III PCD is necrosis, which is the premature death of cells in living tissue, caused by external factors including infections, toxins or trauma. Necrosis is almost always detrimental. Cells that die due to necrosis do not send chemical signals to the immune system, so phagocytes do not locate and engulf the dead cells which in turn lead to a build-up of dead tissue and cell debris. Necrotic tissue generally has to be removed surgically in a process called debridement (NCI, 2011).

Other pathways of PCD are being discovered including necroptosis, the opposite of apoptosis, with less necrotic final result, anoikis is a form of apoptosis which is induced by anchor-dependent cells detaching from the surrounding extracellular matrix. Excitotoxicity is a pathological process by which nerve cells are damaged and killed through excessive stimulation by neurotransmitters (NCI, 2011). There is the regeneration or reconstitution of cells that have undergone apoptosis, but then the cell matter regenerates in another location, and can even go so far as to reproduce a cell layer. A cell layer is a group of cells that attach to one another to produce a larger field of cells. Cancerous cell layers lead to tumors, but healthy cell layers lead to tissue. Certain chemicals have been found to have this characteristic, where the actual cell components are not destroyed, and allowed to in essence be 'reprogrammed' to regenerate. Healthy cells reconstitute their own parts, and resume the cellular cycle, albeit temporarily as these cells are structurally unsound (Alberts, et. al, 2002).



Cell swelling is an indicator of sub-lethal cell damage, where the cell's membranes swell outward as certain substances enter the cell through osmosis, and cause an imbalance of the cell structure. The cell can be recovered, or it can enter apoptosis from this stage. The swelling is an indicator of the accumulation of electrolytes or inducers within the cell beyond the cell's normal

capacity or functioning point. Apoptosis is generally signaled by cell shrinkage or cell swelling (NCI, 2011).

Conductivity/Resistivity

Electrical resistivity (also known as resistivity, specific electrical resistance, or volume resistivity) is an intrinsic property that quantifies how strongly a given material opposes the flow of electric current. A low resistivity indicates a material that readily allows the flow of electric current. Electrical conductivity or specific conductance is the reciprocal of electrical resistivity, and measures a material's ability to conduct an electric current. Many resistors and conductors have a uniform cross section with a uniform flow of electric current, and are made of one material.) The electrical resistivity ρ (Greek: rho) is defined as:

$\rho = R\ A\ \ell$

R is the electrical resistance of a uniform specimen of the material

ℓ is the length of the piece of material

A is the cross-sectional area of the specimen

The reason resistivity is defined this way is that it makes resistivity an intrinsic property. All copper wires, irrespective of their shape and size, have approximately the same resistivity, but a long, thin copper wire has a much larger resistance than a thick, short copper wire. Every material has its own characteristic resistivity – for example, resistivity of rubber is far larger than copper's. The resistance of a given material increases with length, but decreases with increasing cross-sectional area (Giancoli, 1995).

Conductivity is the inverse:

$$\sigma = \frac{1}{\rho} = \frac{J}{E}.$$

ρ is the resistivity of the conductor material,

E is the magnitude of the electric field,

J is the magnitude of the current density

Electrons in an atom do not take on arbitrary energy values. Rather, electrons only occupy certain discrete energy levels in an atom or crystal; energies between these levels are impossible. When a large number of such allowed energy levels are spaced close together (in energy-space)—i.e. have similar (minutely differing) energies—these energy levels together are an "energy band". There can be many such energy bands in a material, depending on the atomic number {number of electrons (if the atom is neutral)} and their distribution (besides external factors like environmental modification of the energy bands). The material's electrons seek to minimize the total energy in the material by going to low energy states; however, the Pauli exclusion principle means that they cannot all go to the lowest state. The electrons instead "fill up" the band structure starting from the bottom. The characteristic energy level up to which the electrons have filled is called the Fermi level. The position of the Fermi level with respect to the band structure is very important for electrical conduction: only electrons in energy levels near the Fermi level are free to move around, since the electrons can easily jump among the partially occupied states in that region. In contrast, the low energy states are rigidly filled with a fixed

number of electrons at all times, and the high energy states are empty of electrons at all times (Giancoli, 1995).

In metals there are many energy levels near the Fermi level, meaning that there are many electrons available to move. This is what causes the high electronic conductivity of metals. An important part of band theory is that there may be forbidden bands in energy: energy intervals that contain no energy levels. In insulators and semiconductors, the number of electrons happens to be just the right amount to fill a certain integer number of low energy bands, exactly to the boundary. In this case, the Fermi level falls within a band gap. Since there are no available states near the Fermi level, and the electrons are not freely movable, the electronic conductivity is very low. A metal consists of a lattice of atoms, each with an outer shell of electrons that freely dissociate from their parent atoms and travel through the lattice. This is also known as a positive ionic lattice. This 'sea' of dissociable electrons allows the metal to conduct electric current. When an electrical potential difference (a voltage) is applied across the metal, the resulting electric field causes electrons to drift towards the positive terminal. The actual drift velocity of electrons is very small, in the order of magnitude of a meter per hour. However, as the electrons are densely packed in the material, the electromagnetic field is propagated through the metal at nearly the speed of light. Near room temperatures, metals have resistance. The primary cause of this resistance is the collision of electrons with the atoms that make up the crystal lattice. This acts to scatter electrons and lose their energy on collisions rather than on linear movement through the lattice. Also contributing to resistance in metals with impurities are the resulting imperfections in the lattice. The larger the cross-sectional area of the conductor, the more electrons per unit length are available to carry the current. As a result, the resistance is lower in larger cross-section conductors. The number of scattering events encountered by an electron passing through a material is proportional to the length of the conductor. The longer the conductor, therefore, the higher the resistance. Different materials also affect the resistance. In electrolytes, electrical conduction happens not by band electrons or holes, but by full atomic species (ions) traveling, each carrying an electrical charge. The resistivity of ionic solutions (electrolytes) varies tremendously with concentration – while distilled water is almost an insulator, salt water is a reasonable electrical conductor. Conduction in ionic liquids is also controlled by the movement of ions, but here we are talking about molten salts rather than solvated ions. In biological membranes, currents are carried by ionic salts. Small holes in cell membranes, called ion channels, are selective to specific ions and determine the membrane resistance (Giancoli, 1995).

Expected Results:

After completion of the sensor, the database and model we hope to have a new scientific advancement that could save many lives. We would love to implement this system and possibly use what we code to make a coexisting app to work with the sensor and user. However, regardless of if this happens or not, we will complete the challenge and compete at the Expo in April.

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